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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/438,989	11/12/1999	YOGESH S. SANGHVI	ISIS-4288	1111

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WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
OWENS JR, HOWARD V	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/10/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/438,989	Applicant(s) SANGHVI ET AL.	
	Examiner Howard V Owens	Art Unit 1623	

-- Th MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6-16-03* .

2a)☒ This action is **FINAL**.. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36,38,39 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36,38,39 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

This action is in response to the request for continued examination filed on 6/16/03.

An action on the merits of claims 1-36, 38, 39 and 44 is set forth below.

Claim Rejections - 35 USC § 102

Claims 1-4, 7, 8, 11-13, 17-36, 38 and 39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stec et al., U.S. 5,883,237.

Claims 1-4, 7, 8, 11-13, 17-21, 23-36, 38 and 39 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound; wherein the oligomeric compound comprises 5 to 50 nucleosides.

Claim 22 is drawn to a pharmaceutical composition containing the compound(s) of claim 1.

The external region is a nucleoside compound connected to either side of the chiral phosphorothioate (the internal region) (p. 27, lines 30-35 of specification). Substituents are defined as groups attached to a 2', 3' or 5' position of a sugar moiety as well as groups attached to the N2 or N6 position of the purine base or the N4 or C5 position of the pyrimidine (p.22, lines 9-20 of specification).

Stec anticipates the claims cited supra as it teaches oligonucleotides containing Rp or Sp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions, nucleosides, flanking the internal region (column 7, lines 14-67). Stec teaches that these oligonucleotides may have substituted bases for both purines and pyrimidines (see columns 11-12) and may range from 1-28 nucleosides (for example, Example 24) which anticipates the oligomeric compound comprising 5 to 50 nucleosides. Stec teaches that these oligonucleotides may be part of a pharmaceutical composition as well (col. 10, lines 30-57).

Claims 1-4, 6-8, 11-13 and 17-36, 38 and 39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hoke et al., is maintained for the reasons of record.

Claims 1-4, 6-8, 11-13, 17-21, 23-36, 38 and 39 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound.

Claim 22 is drawn to a pharmaceutical composition containing the compound(s) of claim 1.

Hoke clearly teaches the chiral phosphorothioate and the presence of flanking oligonucleotides which may contain up to 50 nucleosides with modified bases or sugars (columns 7-9 and claims 2 and 4). Hoke further teaches that it is known in the art that the presence of phosphorothioates within the oligonucleotides imparts greater nuclease resistance and stability over natural phosphodiester oligonucleotides (column 2, lines 4-20) to these oligomeric compounds. Hoke demonstrates the use of these oligonucleotides in a pharmaceutical composition as well, examples 10-12.

Claims 1-14 and 17-36, 38 and 39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cook, U.S. 5,852,188.

Claims 1-14 and 17-21, 23-36, 38 and 39 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound.

Claim 5 is drawn to the compound of claim 1 wherein there is a substituent attached to the 2' position of the nucleoside.

Claim 22 is drawn to a pharmaceutical composition containing the compound(s) of claim 1.

Cook anticipates the claims cited supra as it teaches oligonucleotides containing Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions, nucleosides, flanking the internal region (column 5, line 45 - column 7); wherein the oligonucleotides contains at least 2 nucleosides (wherein the process may be repeated to obtain as many oligonucleotides as necessary- col. 16, lines 39 - 48) with modified bases or sugars in either 2' or 3' positions (columns 6-11 and claims 1-12).

Cook further teaches that it is known in the art that the presence of phosphorothioates within the oligonucleotides imparts greater nuclease resistance and

stability to these oligomeric compounds over natural phosphodiester oligonucleotides (column 1, line 66 - column 2, line 9). Cook teaches the use of these oligonucleotides in a pharmaceutical composition as well (column 12, lines 21 - 44 and col. 11, lines 24-32).

Cook teaches modification of the nucleoside portion of these oligomeric compounds at the 2' position with a variety of groups analogous to those set forth in the instant claims 9 and 29, i.e. lower alkyl, substituted O-alkyl, substituted S-alkyl, NH-alkyl, polyalylamino, substituted silyl, etc. (col. 9, line 37 - col. line 5). Cook also teaches substitution of this 2' position with any group that improves the pharmacodynamic properties of the oligonucleotide wherein pharmacodynamic property comprises enhancing oligonucleotide resistance to degradation.

Applicant argues that because the terms substantially pure are set forth in Cook, the invention as claimed is not anticipated; however, the claim language requires two external regions and an internal region, defined by applicant as a nucleoside compound connected to either side of the chiral phosphorothioate (the internal region) , (p. 27, lines 30-35 of specification). As cited supra, these elements are present in the teachings of Cook and the breadth of applicant's claim language is therefore anticipated by Cook.

Applicant has set forth the term gapmer to purportedly distinguish the claimed compound from the prior art of Stec, Hoke and Cook. However, the term gapmer is actually defined by the structure set forth in the instant claims which consists of ; moreover, the definition of gapmer in the art is that of a central stretch of DNA or phosphorothioate DNA monomers and modified nucleotides. Thus it is clear that the teachings of Cook are still probative to the claimed compound given that Cook teaches modified oligonucleotides with phosphorothioate DNA monomers.

Applicant further asserts that the 3 claimed "regions" are not set forth; however, the specification reveals that these regions are actually 2 different components, an Rp phosphorothioate flanked on either side by a modified/substituted nucleoside. Thus any prior art which teaches a modified oligonucleotide wherein a chiral Rp phosphorothioate is adjoined to modified nucleosides for a chain length of at least 5 is anticipatory.

Applicant has attempted to limit the scope of the prior art by reciting various claims in each of the patents cited; however, the scope of the teachings of the prior art is not limited to claims nor preferred embodiments. As such, the teachings of Stec, Hoke and Cook are still anticipatory for the claims taught supra.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-36, 38, 39 and 44 are rejected under 35 U.S.C. § 103 as being unpatentable over Cook, U.S. 5,852,188 in combination with Alul, U.S. Patent 5,532,130.

Claims 1-4, 6-14 and 17-21 and 23-36, 38, 39 and 44 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound.

Claim 5 is drawn to the compound of claim 1 wherein there is a substituent attached to the 2' position of the nucleoside.

Claims 15 and 16 are drawn to a 2'-5' internucleoside linkage present within the oligomeric compound of claim 1.

Claim 22 is drawn to a pharmaceutical composition containing the compound(s) of claim 1.

Cook teaches oligonucleotides containing Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions, nucleosides, flanking the internal region (column 5, line 45 - column 7); wherein the oligonucleotides contains at least 2 nucleosides (wherein the process may be repeated to obtain as many oligonucleotides as necessary- col. 16, lines 39 - 48) with modified bases or sugars in either 2' or 3' positions (columns 6-11 and claims 1-12).

Cook further teaches that it is known in the art that the presence of phosphorothioates within the oligonucleotides imparts greater nuclease resistance and stability to these oligomeric compounds over natural phosphodiester oligonucleotides (column 1, line 66 - column 2, line 9). Cook teaches the use of these oligonucleotides in a pharmaceutical composition as well (column 12, lines 21 - 44 and col. 11, lines 24-32).

Cook teaches modification of the nucleoside portion of these oligomeric compounds at the 2' position with a variety of groups analogous to those set forth in the instant claims 9 and 29, i.e. lower alkyl, substituted O-alkyl, substituted S-alkyl, NH-alkyl, polyalylamino, substituted silyl, etc. (col. 9, line 37 - col. line 5). Cook also teaches substitution of this 2' position with any group that improves the pharmacodynamic properties of the oligonucleotide wherein pharmacodynamic property comprises enhancing oligonucleotide resistance to degradation.

Although Cook does not teach the presence of a 2', 5' internucleoside linkage within the oligomeric compound, Alul teaches that 2'-5' linkages confer resistance to both exo and endonucleolytic degradation, serve as modulators for gene expression and ; moreover that these 2'-5' linkages may be combined with 3'-5' oligomers (column 6, line 46 - col. 8) which adequately bridges the nexus between the prior art and the invention as claimed.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to incorporate a 2'-5' internucleoside linkage within an oligomer comprising a 3'-5' internucleoside linkage.

A person of ordinary skill in the art would have been motivated to incorporate a 2'-5' internucleoside linkage for the art recognized benefits of increasing nuclease resistance and regulating gene expression through sequence specific hybridization of DNA or mRNA.

Applicant has set forth the term gapmer to purportedly distinguish the claimed compound from that of the prior art. However, the term gapmer is actually defined by the structure set forth in the instant claims which consists of ; moreover, the definition of gapmer in the art is that of a central stretch of DNA or phosphorothioate DNA monomers and modified nucleotides. Thus it is clear that the teachings of Cook are still probative to the claimed compound given that Cook teaches modified oligonucleotides with phosphorothioate DNA monomers.

Applicant has attempted to limit the scope of the prior art by reciting various claims in each of the patents cited; however, the scope of the teachings of the prior art is not limited to claims nor preferred embodiments.

Applicant further asserts that the 3 claimed "regions" are not set forth; however, the specification reveals that these regions are actually 2 different components, an Rp phosphorothioate flanked on either side by a nucleoside. Thus any prior art which teaches a modified oligonucleotide wherein a chiral Rp phosphorothioate is adjoined to modified nucleosides for a chain length of at least 5, supports the conclusion of obviousness.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Howard V. Owens
Patent Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (703) 306-4538 . The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner signing this action, James O. Wilson can be reached on (703) 308-4624 . The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.